REMARKS/ARGUMENTS

Claims 4, 7, 22, 55, 56 and 65 have been canceled to correspond with the elected invention.

Claims 1, 19, 34 and 49 have been revised to include the feature of a heavy chain variable region with a heavy chain constant region modified at positions 250 and 428. The revision better tailors the claims for currently contemplated commercial embodiments of the invention and so are made for business reasons. The revisions are not in acquiescence to any rejection of record. Applicants reserve the right to pursue the subject matter no longer within the scope of the amended claims in a divisional or other continuing application without prejudice.

Claims 1, 8-12, 15-17, 19, 24-28, 31, 35-38, 40-43, 49, 57, 58, 60-64, and 67-69 have been revised to expressly recite the inherent EU numbering system used to identify amino acid residues 250 and 428.

Each of claims 5 and 23 has been revised in their claim dependencies and to include a reference to a naturally occurring human IgG1 class antibody.

Claim 6 has been revised to recite corresponding SEQ ID NOs. Support is present at least in Figure 3A and its brief description in the instant application.

Claims 8, 11 and 15 have been re-written to be in independent form, with all the features of previous claim 1 from which claims 8, 11 and 15 were dependent. Claims 16 and 17 have been revised to be dependent from claim 15. Similarly, claims 24, 27 and 31 have been re-written to be in independent form, with all the features of previous claim 19 from which claims 24, 27 and 31 were dependent. Claims 32 and 33 have been revised to be dependent from claim 31. Also, claims 36 and 41 have been revised to be in independent form, with all the features of previous claims 34 and 39, respectively, from which claims 36 and 41 were dependent.

Claim 57 has been revised to be directed to a method for preparing an antibody of claim 1. Similarly, claim 58 has been revised to be directed to a method of producing an antibody with all the features of claim 1. These revisions are made for reasons related to the Restriction Requirement of record and the elected invention. These amendments allow for rejoinder of claims 57-64 and 67-69 as described below and are not in acquiescence to any rejection of record. Applicants reserve the right to pursue the subject matter no longer within the scope of the amended claims in a divisional or other continuing application without prejudice.

Claims 15-17, 31-33, 54, 57-64 and 67-69 have been held as withdrawn from consideration as being to a non-elected invention.

No new matter has been introduced, and entry of the revised claims is respectfully requested to leave claims 1-3, 5, 6, 8-12, 15-21, 23-28, 31-43, 49, 52-54, 57-64, and 67-69 pending.

Restriction Requirement/Elected Invention

Applicants confirm the election of Group I, claims 1-3, 5, 6, 8-12, 18-21, 23-28, 34-43, 49, 52, and 53, as well as the election of the isotype IgG2 and positions 250 and 428, EU numbering, of the constant region as glutamine and leucine, respectively.

Applicants also acknowledge the Examiner's recognition of the standards for rejoinder as set forth at MPEP 821.04. Applicants respectfully point out that claim 57 as well as claims 58-64 and 67-69 are subject to those rejoinder rules. Applicants respectfully request that the Examiner acknowledge the applicability of the rejoinder rules to claims 57-64 and 67-69 in the next Office communication.

Applicants also wish to express their understanding that the search and examination of the elected species has been extended beyond the election of the IgG2 isotype and the specific substitution of glutamine and leucine at positions 250 and 428, respectively. This is consistent with the nature of an election of species, where after search and examination of the elected species, the search and examination proceeds to one or more additional species.

Specifically, Applicants acknowledge the extended search and examination reflected in the consideration and examination of the "OST577-IgG1" subject matter in claim 6; and the alleged rejections based on Martin et al. and Martin et al. in view of Reff et al. and Ogata et al., which rejections are not limited to any IgG isotype. For example, the alleged rejections based on Martin et al., alone or in view of Reff et al. and Ogata et al., appear to include all possible IgG subclasses.

The breadth of the search and examination is also evidenced by the Examiner's search strategy and search results for the instant application available through the U.S. Patent and Trademark Office (PTO) website. The strategy and results were not limited to the IgG2 isotype. Moreover, the sequence searches encompassed all possible substitutions at positions 250 and 428 rather than just the specific glutamine and leucine substitutions at those two positions, respectively. This is reflected in the search results, where the amino acid search query used the heavy chain constant region with "X" for both

the position 250 threonine and the position 428 methionine to allow for all possible amino acid substitutions to be found.

In light of the broad search and examination that has been conducted, Applicants acknowledge the search and examination of the claims for IgG2 and other IgG isotypes as well as all possible substitutions at positions 250 and 428.

Formal Matter Regarding Trademarks

The specification has been revised as indicated above to include references to trademarks where believed to be applicable. Applicants have also utilized this opportunity to correct certain typographical errors in the text of the specification. No new matter has been introduced, and entry of the revised paragraphs is respectfully requested.

Alleged Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 5, 6, 8-12, 18-21, 23-28, 34-43, 49, 52, and 53 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because they recite amino acid residue positions without reciting the numbering system.

Applicants respectfully traverse because a skilled person's consideration of the claims in light of the specification would readily recognize that the numbering system used was the EU system. Applicants appreciate the Examiner's suggestion to expressly recite the EU numbering to reflect the inherent feature of the claims. The claims have been so revised, without altering the intended claim scope, and Applicants respectfully request that this rejection be withdrawn.

Claim 6 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to recitation of "OST577-IgG2M3" and "OST577-IgG1". Applicants respectfully traverse because these terms are defined in the specification at least in relation to Figure 3A and by its brief description. Applicants appreciate the Examiner's suggestion to include SEQ ID NOs to reflect the inherent structural features of these terms. The claims have been so revised, with support present as described above. No change in claim scope is believed to have occurred, and Applicants respectfully request that this rejection be withdrawn.

Alleged Rejection Under 35 U.S.C. § 112, First Paragraph

Claim 6 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter "not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

Applicants have carefully reviewed the statement of the rejection and understand it to be directed to the recitation of the "OST577-IgG2M3" and "OST577-IgG1" antibodies in claim 6. Applicants further understand it to include the Examiner's suggestion for either a biological deposit of the antibodies under the Budapest Treaty or inclusion of the sequence of the antibodies in their entireties.

Applicants respectfully point out that claim 6 has been revised above to include SEQ ID NOs representing the heavy and light chain sequences that define an antibody molecule. The well known structure of antibody molecules is shown in Figure 1 of the instant application. Therefore, Applicants believe that contrary to the asserted basis for the instant rejection, no issue of enablement regarding claim 6 is present. Accordingly, reconsideration and withdrawal of the instant rejection is respectfully requested.

Alleged Rejection Under 35 U.S.C. § 102

Claims 1, 8-12, 18, 19, 24-28, 34-43, 49, 52, and 53 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Martin et al. as evidenced by Hinton et al. Applicants have carefully reviewed the statement of the rejection and respectfully traverse because no *prima facie* case of anticipation has been presented.

As an initial matter, Applicants point out that the instant rejection must be based on Martin et al. alone. The Hinton et al. reference is after the filing date of the instant application and so cannot serve as a basis for rejection under 35 U.S.C. § 102(b). Moreover, Hinton et al. also cannot be used to add disclosure to that by Martin et al. The standard set forth at MPEP 2131.01, and the court decisions cited therein, provide only three possible proper reasons to rely on an extra reference in a 35 U.S.C. § 102 rejection. None of the three relate to an extra reference (such as Hinton et al.) discussing a species not disclosed in the primary reference (Martin et al.).

The instant statement of the rejection, however, does not specify which of the three reasons from MPEP 2131.01 allows for the inclusion of Hinton et al. Instead, the statement of the rejection alleges that Hinton et al. describe subject matter as follows:

> "IgG mutants T250Q and M428L show increased binding to FcRn at pH 6.0 and no binding at pH 7.5 (see entire document, particularly page 6215, left column) and with an in vivo mean serum clearance rate about 1.8-1.9 fold lower than that of the corresponding unmodified antibody (e.g. see page 6216, left column)."

The above quote is clearly based upon Hinton et al.'s discussion of the particular "IgG mutants T250Q and M428L". But neither of these particular mutants are reported or discussed by Martin et al. So Hinton et al. is cited for its discussion of two species not found in Martin et al. This inclusion of Hinton et al. is improper because 1) it attempts to inject the discussion of two particular species from Hinton et al. into the separate content of Martin et al.; and 2) it is irrelevant to the actual discussion in Martin et al., which does not include either of the two species. Accordingly, the reliance on Hinton et al. to allege an inherent property of subject matter discussed in Martin et al. is in error.

In light of the above, Applicants respectfully point out that inclusion of Hinton et al. lacks a proper basis and is improper. Because Martin et al. do not discuss the two particular species of Hinton et al., the two species and their characteristics cannot be add to Martin et al. Accordingly, the inclusion of Hinton et al. should be withdrawn, and this rejection may only be based on Martin et al. alone.

Moreover, Applicants point out that claims 1, 19, 34, 39, and 49 have been revised to recite both a heavy chain variable region and a heavy chain constant region. These claims are directed to antibody polypeptide(s) that include a heavy chain variable region. Additionally, claims 6, 8-12, 15-17, 24-28, 31-33, 36-38, 41-43, and 49 feature specific sequences and amino acid residues. Claims 52 and 53 are directed to fragments of a human antibody.

This is in contrast to Martin et al.'s discussion of the use of a mutant, and heterodimeric, rat IgG2a Fc-only region to form a complex with rat FcRn as a model system (see page 867, right column, first full paragraph). There is no disclosure by Martin et al. of any variable region in their Fc-only polypeptides, and no disclosure of any fragment of a human antibody.

It is well settled law that a case of anticipation requires a cited reference to teach every element of a claim (see MPEP 2131 and the cases cited therein). Given the factual differences between the claims and the Martin et al. reference, Applicants respectfully submit that no case of anticipation is present, and the instant rejection should be withdrawn.

Moreover, Applicants respectfully point out that it is also well settled that generally, a genus does not anticipate a species, or a collection of species, that is distinct from the genus. Martin et al., only discusses a *genus* of possible changes to make in heterodimeric, rat Fc-only molecules. In the case of position 250 as a representative example, Martin et al. discuss nine other amino acid positions in a second "*category of candidates for mutagenesis*" for a total of 10 positions to randomly mutagenize, *alone or in combination*. This represents a genus containing an enormous number of possible modified heterodimeric Fc-only molecules.

Claims 8, 11, 24, 27, 36, and 41, however, are directed to a subgenus, or multiple individual species, of specific modifications that are distinct from the Martin et al. genus. Where do Martin et al. disclose these specific subgenera or species? In the absence of specific disclosure by Martin et al., the claimed species are simply not taught, and therefore not anticipated, by the cited reference.

In light of the foregoing, Applicants respectfully submit that no *prima facie* case of anticipation is present, and so this rejection may be properly withdrawn.

Alleged Rejection Under 35 U.S.C. § 103

Claims 1-3, 5, 6, 20, 21, and 23 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Martin et al. (as discussed above) in view of Reff et al. and Ogata et al. Applicants have carefully reviewed the statement of the rejection and respectfully traverse because no *prima facie* case of obviousness has been presented.

It is well settled law that a *prima facie* case of obviousness requires a suggestion or motivation to modify the cited references, the presence of a reasonable expectation of success in making the modification, and the disclosure or suggestion of all claim features (see MPEP 2143 to 2143.03 and the cases cited therein).

The instant statement of the rejection, however, fails to comply with all three of these requirements. With respect to a suggestion or motivation, the rejection alleges that it is present because

> "Martin et al. teach that mutations at Fc region including positions 250 and 428 of an antibody would enhance its binding to FcRn resulting in prolonged serum half-life; and Reff et al. teach method of making human antibody that is better tolerated in treating human patients and Ogata et al. teach OST577 antibody delays HBV infection and hepatitis in experimental animal."

Applicants respectfully point out, however, that the above quote appears to be simply a listing of alleged teachings without any indication of why the teachings should be combined. For example, no suggestion to motivation to combine Martin et al. with the other references is present because, and as discussed above with respect to the asserted anticipation based on Martin et al., Applicants strongly disagree that "Martin et al. teach that mutations at Fc region including positions 250 and 428 of an antibody would enhance its binding to FcRn resulting in prolonged serum half-life" (underlining added).

A review of the relevant paragraph of Martin et al., starting on page 873 and ending on page 875, shows that the discussion of positions 250 and 428 therein merely provides a hope of modifications that "may yield" (in the case of position 250 and others) or "could result" in (in the case of position 428 and others) increased FcRn binding. With the use of phrases like "may yield" and "could result", Martin et al. do not meet the required standard for an adequate motivation to make and use molecules with the proffered modifications.

The mere offer of modifications to try is also shown by the fact that Martin et al. do not report any preparation or study of molecules modified at the indicated positions. Instead, the hypothetical modifications are presented in the context of a heterodimeric, rat IgG2a Fc-only molecule for use in the Martin et al. model system. Such a system does not provide the necessary reasonable expectation of success in cases of a heavy chain constant region combined with a variable region. Therefore, there is no expectation of success in modifying an antibody of claim 1-3, 5, 6, 20, 21, and 23.

In light of the foregoing, Applicants respectfully submit that no prima facie case of obviousness is present because no adequate motivation to combine the cited references to arrive at the claimed invention, and no reasonable expectation of success in making such a combination, are present. Accordingly this rejection is misplaced and may be properly withdrawn.

Alleged Rejections Based on Obviousness-Type Double Patenting

Claims 1-3, 5, 8-10, 12, 19-21, 23-28, 34-43, 49, 50, and 53 were provisionally rejected as unpatentable over claims 1-8, 13, and 15 of commonly assigned, copending application 10/822,300. The statement of the rejection points out that a Terminal Disclaimer may be used to obviate this provisional rejection.

Applicants respectfully request that this provisional rejection be held in abeyance until the claims are otherwise allowable and the issue of obviousness-type double patenting is held as remaining.

Claims 1-3, 5, 8-10, 12, 18-21, 23-28, 34-43, 49, 50, and 53 were provisionally rejected as unpatentable over claims 1-5, 7-13, 15, and 17-19 of commonly assigned, copending application 10/966,673. The statement of the rejection points out that a Terminal Disclaimer may be used to obviate this provisional rejection.

Applicants respectfully request that this provisional rejection be held in abeyance until the claims are otherwise allowable and the issue of obviousness-type double patenting is held as remaining.

Alleged Lack of Patentable Distinction

Claims 1-3, 5, 8-10, 12, 18-21, 23-28, 34-43, 49, 50, and 53 were held as "directed to an invention not patentably distinct" from claims 1-5, 7-13, 15, and 17-19 of commonly assigned, copending application 10/966,673. The statement of the allegation appears to request a showing that the instant application and copending application 10/966,673 were commonly owned at the time *the invention in the instant application was made*.

Applicants respectfully point out, however, that the instant application has a filing date of October 15, 2003 while copending application 10/966,673 has a *later* filing date of October 15, 2004. Accordingly, Applicants are uncertain as to the basis of the determination that the invention in application 10/966,673 was in existence, and therefore could be co-owned, at the time of the instant invention.

Despite the uncertainty, and in the interest of advancing prosecution, Applicants submit that the invention of copending application 10/966,673 was commonly assigned, or subject to the same duty to assign, with the invention of the instant application at the time the invention in copending application 10/966,673 was made.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6100.

Respectfully submitted,

'Kawai Lau, Ph.D.
Reg. No. 44,461

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 858-350-6100
Fax: 415-576-0300
KL:ps 60758136 v1